Thomas X. White
Associate Vice President
Manufacturing and Quality Control
Scientific and Regulatory Affairs

PhRMA

November 28, 2000

00 NOV 30 AM 8:37
2039

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 00D-1424; Draft Guidance for Industry on Analytical Procedures and Methods Validation: Chemistry, Manufacturing and Controls Documentation; Notice of Availability Appearing in the Federal Register for August 30, 2000, (65 FR 52776)

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, happier and more productive lives. Investing more than $26 billion in 2000 in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

The FDA draft guidance is intended to provide recommendations to sponsors of New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), Biological License Applications (BLAs), Product License Applications (PLAs) and supplements to those applications in regard to assembling information, submitting samples and presenting data to support analytical procedures and methods applicable to drug substances and drug products in their applications. If finalized, the proposed draft guidance would replace an existing FDA Guideline for Submitting Samples and Analytical Data for Methods Validation that has been in effect since 1987. The draft guidance also references relevant FDA approved International Conference on Harmonization (ICH) guidances, including Q2A Text on Validation of Analytical Procedures (March 1995) and Q2B Validation of Analytical Procedures (November 1996).

PhRMA members have utilized those previously approved guidances to develop the necessary documentation to support the analytical procedures that they develop for NDAs, ANDAs, PLAs, BIAs and supplements thereto. Our members will have to assure that their procedures, methods, systems, sample preparation and handling, and analytical data management will comport with this new, broadened and divergent guidance if it is finalized. Therefore, PhRMA is vitally interested in assuring that the

00D-1424

C 18

guidance reflects a sound scientific basis, as well as a practicable approach from the standpoint of the applicants' operations and the FDA reviewers' requirements to assess the safety and effectiveness of new drugs and biologics.

Our members have noted serious objections to the issuance of this proposed draft guidance.

- The draft was apparently developed without any collaboration with the affected industry. In PhRMA's view, the Agency should have included and taken advantage of collaborative forums or workshops with industry scientists before developing a new documentation guidance for analytical procedure validation.

- The draft contains several important inconsistencies with harmonized guidances adopted under the International Conference on Harmonization for Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) process. Such inconsistencies would result in future disharmony within the ICH, conflict with other approved FDA guidances and, in general, result in confusion and misinterpretations regarding appropriate technical documentation for information on analytical procedures and their validation as part of drug application submissions.

- Finally, the proposed draft guidance goes well beyond what is necessary for documentation for analytical procedure validation. The thirty-three page draft guidance is much too detailed; many provisions are not scientifically based and need clarification. As a result of such unnecessary detail, the regulatory burden associated with submissions of documentation under this draft guidance will be greatly increased without any real benefits gained for anyone, including FDA chemistry reviewers.

To assist the FDA in the further development of this draft guidance, PhRMA is submitting the enclosed general comments, specific comments on a line-by-line basis and a set of editorial comments, also line-by-line. These comments have been developed following a thorough review of the draft guidance by analytical scientists and regulatory professionals from our member firms.

PhRMA, however, strongly recommends that this draft guidance be withdrawn and that the Agency initiate a collaborative forum or workshop approach that would utilize the existing approved FDA guidances applicable for this topic and determine what is necessary to have the guidance reflect acceptable practice. Such an approach would also help to assure consistency with other related FDA or ICH guidances and especially with the most recently approved ICH Common Technical Document

Guidance for the Quality or Chemistry, Manufacturing Controls Section of New Drug Applications.

PhRMA appreciates the FDA consideration of these comments and would welcome an opportunity to participate in any collaborative mechanism that the agency deems appropriate to improve and make more relevant a new draft guidance for this important topic.

Sincerely,

Thomas X. White

Enclosures: General Comments
Specific Comments
Editorial Comments

Enclosure

General Comments:

The harmonization of regulatory requirements for the CMC controls is critical to achieving the goal of harmonized content under the ICH M4 Guideline: *The Common Technical Document.* Applicants will never be able to write a single document that is suitable for submission in all three ICH regions in the absence of such fundamental harmonized requirements on this topic. Therefore, FDA's publication of draft guidance that is contrary to ICH principles is of great concern.

In particular, harmonized regulatory requirements are needed for the reporting of impurities (according to the ICH definition, "impurities" includes both synthetic impurities and degradation products), and the setting of specifications based on the reported data. The Agency has chosen to set aside the ICH practice of reporting impurities that are above a "Reporting Threshold". This request for more detailed information, reported at levels equal to or greater than the Quantitation Limit(s), is not supported from a safety or efficacy perspective.

Modular documents prepared according to the ICH *The Common Technical Document* (appropriately cross-referenced) minimize the resources needed for efficient preparation and review of a dossier, and are thus in accordance with stated FDA goals. This draft guidance requests detailed information included in the section on Analytical Procedures and Controls that is generally fully discussed in other sections of an application. Such requests would result in redundancies and inefficiencies contradictory to the those goals.

Additionally, there are many detailed requests that go well beyond current practice. For example, reporting of Raw Data is requested in several sections of the draft guidance. The term "Raw Data" needs to be clearly defined and the purpose for this request clarified. The compliance of the results based on the raw data is better addressed at time of pre-approval inspection. Also, we question the need for the entire section XI. Methodology. Information on the important characteristics of varied types of analytical techniques is available in the USP, scientific literature and other sources. Such detailed submission information requests are unnecessary. Indeed, our members have noted that the only section of the draft guidance with demonstrable utility is Section X. Methods Validation Package: Contents and Processing. That section, along with the adopted ICH guidances applicable to Analytical Procedure Validation provide an appropriate point of departure for further consideration of necessary guidance for this topic.

Within the context of acceptable analytical practices as contained in ICH, FDA, compendial and other publications, it is important to preserve a certain level of flexibility to conduct optimal scientific studies. Each new product application is unique. This draft guidance should refrain from excessively detailed requests that detract from the analytical science, and implement outcome-based criteria for evaluating the scientific results.

PhRMA believes that the FDA missed an opportunity to secure a sound basis for this draft guideline by utilizing an almost complete internal development process for its preparation. There are numerous examples where early interaction with the scientists from the regulated community by the FDA results in a very scientifically based document that has practicable utility to both the industry sponsors and the reviewing chemists at the Agency. Unfortunately, for whatever reason, the FDA chose not to collaborate with industry stakeholders in the development of this subject draft guidance. PhRMA urges the FDA to reevaluate this draft document and utilize the "Good Guidance Practice" principles that call for collaboration with interested parties in the development of significant guidances.

Enclosure

Specific Comments:

In most cases the specific language from the draft guideline that is being cited is given, followed by PhRMA commentary and, in some cases, specific recommendations for improving the draft, or revised language for the provision.

Lines 89 and 226-227 Relative Importance of Test Procedures

"All analytical procedures are of equal importance from a validation perspective." "All analytical procedures should be fully developed and validation completed when the NDA, ANDA, BLA, or PLA is submitted."

Not all analytical procedures are "validated" with an equal level of rigor. Some procedures are "calibrated" but no validation study is performed. Examples include: X-ray diffraction, pH, Water by Karl Fischer, TGA, Optical Rotation, Weight-Based Measurements, etc. Additionally, analytical procedures for testing intermediates, starting materials, excipients, etc., may be validated via less extensive experimental studies.

This section should be revised to reflect that validation should be performed when and as appropriate. Within the context of acceptable analytical practices as contained in ICH, FDA, compendial and other publications, it is important to preserve a certain level of flexibility in how control of the analytical procedure is demonstrated.

Line 136-143 Types of Reference Standards

"When there is no official source, a reference standard should be of the highest possible purity and be fully characterized. A working standard (i.e., in-house or secondary standard) is a standard that is qualified against and used instead of the reference standard."

PhRMA recommends that FDA adopt the terminology used in the ICH Q7A GMPs for Active Pharmaceutical Ingredients Guidance on "primary reference standards", "in-house primary standards" and "secondary reference standards" (reference standards for a drug substance, that may be internally generated). Some of these approaches also apply to other types of reference materials, but some are not applicable.

The term "highest possible purity" implies that some purification steps were taken, which we believe is ***not*** universally appropriate. USP reference standards are typically not "highly purified", but are "representative".

PhRMA recommends revising the wording to:

> "When there is no official source, an in-house primary reference standard should be fully characterized. A secondary reference standard is a substance that is qualified against the primary reference standard and used instead of it."

Line 155-162 Characterization of a Reference Standard

"A reference standard that is not obtained from an official source should be of the highest purity that can be obtained by reasonable effort, and it should be thoroughly characterized to ensure its identity, strength, quality, purity and potency. The qualitative and quantitative analytical procedures used to characterize a reference standard are expected to be different from, and more extensive than, those used to control the identity, strength, quality, purity, and potency of the drug substance or the drug product. Analytical procedures used to characterize a reference standard should not rely solely on comparison testing to a previously designated reference standard."

PhRMA recommends that FDA adopt the ICH Q7A guidance terminology, revising the wording to:

> "An in-house primary reference standard (not obtained from an official source) should be thoroughly characterized to ensure its identity, strength, quality, purity, and potency. The qualitative and quantitative analytical procedures used to characterize a primary reference standard are expected to be more extensive than those used to control the identity, strength, quality, purity, and potency of the drug substance or the drug product. Analytical procedures used to characterize an in-house primary reference standard should not rely solely on comparison testing to a previously designated reference standard."

It is agreed that the quantitative and qualitative procedures used to characterize an in-house primary reference standard (not obtained from an official source) need to be more extensive than those used to control the drug substance/drug product. As written the guidance would imply that all procedures used to characterize the primary reference standard are *different from* those used to control drug substance/drug product. FDA needs to clarify if the intent of this guidance is that "different" tests are required to characterize such reference standards, or only that "additional" tests are required. Some procedures used during characterization may be applicable as quality control tests for the drug substance/drug product. The implication that all procedures used during characterization be different than those used to control the drug substance/drug product is inappropriate.

Earlier in the same section, it is stated that USP standards do not require additional characterization. Yet, this testing would require extensive characterization of a secondary reference standard, even if its response for a given test were the same as the USP primary reference standard. The need for this requirement is unclear.

Line 183-184 Reference Standard Chemical Attribute Information

"Information to substantiate the proof of structure should include appropriate analytical tests, such as elemental analysis, infrared spectrophotometry (IR), ultraviolet

spectrophotometry (UV), nuclear magnetic resonance spectroscopy (NMR), and mass spectrometry (MS), as well as applicable functional group analysis."

It is not clear what is meant by "applicable functional group analysis." Does this refer to old, qualitative, wet chemical tests for various functional groups? Assuming good quality data has been collected from the previously listed techniques (IR, UV, NMR, etc.), there is no reason to perform the wet chemical tests. Certainly the modern analytical methods provide more accurate and more detailed information.

Line 189-190 Reference Standard Physical Constant Checks

"Appropriate physical constants such as melting range, boiling range, refractive index, dissociation constants (pK values), and optical rotation."

Once the structure has been established, checks of physical constants should be viewed as confirmatory. Extensive physical characterization on each reference standard is redundant to proof of structure and confirmation of purity. Physical testing as appropriate for the intended use should be performed (e.g., demonstration of correct polymorph for standards to be employed in x-ray analysis).

Line 283-287 Non-chromatographic System Suitability

"System suitability testing is recommended as a component of any analytical procedure, not just those that involve chromatographic techniques. ...For example, titration analytical procedures should always include the evaluation of a blank (commonly referred to as a blank titration)."

The example provided is not appropriate, since the titration of a blank frequently is part of the analytical determination. An alternative example may involve the use of rotation standards for polarimetry, viscosity reference materials, pH standardization, etc.

Additionally, the wording of the guidance should be revised to clarify that a calibration check with suitable standard materials may be used instead of "system suitability testing" of non-chromatographic systems.

Line 301-303 Procedure

"A step-by-step description of the procedure should be provided. The description should include, where appropriate, equilibration times, injection sampling sequence, and system suitability or start-up parameters. Unusual hazards should be identified."

This section requests a level of detail that we feel is excessive in many cases. Only the details necessary to successfully execute the procedure should be described. Methodology that performs in a robust manner may be described more generally. Mention of system suitability is redundant here, since it is discussed in section E.

PhRMA recommends replacing the middle sentence with the following:

> "The description should include experimental details that are necessary to successfully execute the procedure."

Lines 326-327, 332-335, 464, and 513-514 Reporting of Impurities Results

"...in the analytical procedures for impurities in the drug substance and drug product. The detection limit (DL) or quantitation limit (QL) should be stated, as appropriate."

"The total organic impurities for the drug product or drug substance is the sum of all impurities equal to or greater than their individual QL. See recommendations regarding appropriate QLs in FDA impurities guidances (see references)."

"The impurity profile should be assessed at the quantitation limit..."

"The quantitation limit ...should be stated."

"The quantitation limit ...should be reported."

Quantitation Limit versus Reporting Threshold:

PhRMA objects strongly to these guidance sections that are not consistent with approved ICH guidances. It is extremely important that these provisions be based on the harmonized ICH guidances to avoid confusion, disharmony and misinterpretation.

The Quantitation Limits of modern analytical procedures are often lower (sometimes much lower) than the ICH reporting thresholds defined in ICH Q3A(R) and Q3B(R) for organic impurities in a drug product or drug substance. The proposed FDA requirement to report at levels equal to or greater than the Quantitation Limit(s) of an analytical procedure is inconsistent with the ICH reporting threshold practices. We would like to emphasize that the harmonization of regulatory requirements for the reporting of impurities, and the setting of specifications based on the reported data, is critical to achieving the goal of harmonized content under the ICH M4 Guideline: *The Common Technical Document.*

The ICH Q3A(R) Guideline states: "Levels of impurities which are not more than (<=) the reporting threshold in Attachment 1 need not be reported." Both ICH Q3A(R) and Q3B(R) Guidelines state: "All impurities at a level greater than (>) the reporting threshold should be summed and reported as Total Impurities." The Reporting Threshold is defined as "A limit above which an impurity needs to be reported."

The Agency has chosen to set aside this accepted practice and request far more detailed information. This request is not supported from a safety or efficacy perspective. It raises concern about the status of the ICH Guidelines within FDA.

The precision of an analytical test procedure is approximately related to the analyte concentration. Thus it is desirable to keep the concentration of the active substance in the matrix as high as possible to keep the analytical variances at a minimum. [T. Layloff and P. Motise, *Pharm. Tech.*, 122-132 (1992)] Modern measurement instrumentation may achieve very low Quantitation Limits (QL) and Detection Limits (DL), and it may be capable of generating detailed profiles of organic impurities present at a level that is an order of magnitude below the ICH reporting level, which has no impact on safety nor efficacy. Using such a sensitive test procedure and high concentration test solutions, minute amounts of large numbers of impurities could be quantitated with high precision. The requirement to report and track all of these impurities (that are of no safety concern) at or above the QL would result in an excessive and unnecessary regulatory burden. Companies would be penalized by utilizing good science.

A less sensitive test procedure, with QL approximately equal to the ICH Reporting Threshold, would be capable of quantitatively measuring the impurities according to the FDA and ICH guidelines. Its measurement precision would be reduced in comparison with the above approach. Such an acceptable test procedure would minimize the burden of reporting and tracking many organic impurities. There would be no motivation for companies to fully exploit their capabilities to enhance the measurement sensitivity and precision.

Therefore an analytical procedure should contain instructions for evaluating data versus the reporting threshold as per the ICH guidance. There is no value in including the QL or the DL in the analytical procedure. The quantitation limit and the detection limit are instrument dependent parameters and are more appropriately reported in the validation report for the procedure. The incorporation of a sensitivity check as a system suitability test for procedures used to determine impurity levels is a more appropriate approach to ensuring that the method and system are capable of achieving the proper sensitivity required for the analysis. The method validation report should demonstrate that the QL and DL are no greater than the reporting threshold.

PhRMA strongly recommends that FDA revise this draft guidance to reflect the harmonized reporting threshold, thereby encouraging the development of sensitive methods. PhRMA also recommends the addition of a definition of "Reporting Threshold" to the Glossary.

Total Organic Impurities:

Discussion of impurities in the drug product should be revised and separated from the discussion of Total Organic Impurities in the drug substance. The ICH definition of "impurity" includes both impurities arising from the synthesis of the drug substance and also degradation products.

PhRMA recommends that FDA revise the Total Impurities discussion to read:

> "The total organic impurities for the drug substance is the sum of all impurities greater than (>) the reporting threshold. For the drug product, all degradation products at a level greater than (>) the reporting threshold should be summed and reported as "Total Degradation Products".

This change would be consistent with section 1.3 Scope of the Q3B(R) Guideline, where it is stated that "Impurities present in the new drug substance need not be monitored or specified in drug products unless they are also degradation products (see ICH Q6A guidance for setting specifications)." This is also consistent with the ICH Q6A Guideline, which states in section 3.2.2 d): "Acceptance limits should be stated for individual specified degradation products, which may include both identified and unidentified degradation products as appropriate, and total degradation products. Process impurities from the new drug substance synthesis are normally controlled during drug substance testing, and therefore are not included in the total impurities limit."

Line 342-344 Reporting for Biologicals

"The above reporting information may not be strictly applicable to all products (e.g., biological, biotechnological, botanical, radiopharmaceutical drugs), but any significant process and product-related impurities should be determined and reported."

This paragraph should be either deleted or revised.

The current vague wording may be interpreted to signify that less rigorous requirements apply for BLAs. There is no scientific rationale for less rigorous requirements for BLAs. Impurities in biologicals should be described and controlled in sufficient detail according to an appropriate Reporting Level (per ICH).

Alternatively, the wording should be revised to provide clear guidance with information on the different requirements for BLAs.

Line 392-393 Submitted Raw Data

"Representative calculations using submitted raw data, to show how the impurities in drug substance are calculated."

The need to include representative calculations using submitted raw data seems unnecessary. As long as formulae are provided with the terms clearly defined, there should be no need for representative calculations.

A complete description of any calculations used to determine impurity levels should be provided in the test procedure, not in the method validation report. The correctness of specific calculations based on raw data is better addressed at time of pre-approval inspection.

For most applicants, the "raw data" that is requested is electronic in nature. The guidance inappropriately uses the term raw data.

PhRMA recommends that this provision be removed. If it is retained or revised, we suggest that it more appropriately belongs in Section X: Methods Validation Package.

Line 402-408 Solid State and Impurity Information

"Methods validation information should also include: ... For drug substances:

- A discussion of the possible formation and control of polymorphic and enantiomeric substances.

- Identification and characterization of each organic impurity, as appropriate. This information may not be needed for all products (e.g., botanicals). Other impurities (e.g., inorganics, residual solvents) should be addressed and quantitated."

The draft guidance seems to be confusing the contents of the methods validation package with the contents of the methods validation report. Detailed discussion of these two topics is inappropriate for a methods validation report. Reference to the result of the study on solid state properties or impurities may be appropriate, if the validation report corresponds to the test procedure that controls this property of the drug substance. The use of cross-references should be encouraged to minimize redundancies, and to facilitate efficient preparation and review of an application.

Line 414-415 List of Known Impurities

"A list of known impurities, with structure, if available, including process impurities, degradants, and possible isomers."

The term "possible isomers" is vague and needs to be better defined. It could be interpreted to include a very large number of compounds.

Line 428-429 Additional Validation Parameters and Detail Beyond ICH

"ICH Q2A and Q2B address almost all of the validation parameters. Areas that should be provided in more detail are described below."

We question the need for the detailed discussion in this section. This wording implies that ICH guidances are incomplete. Robustness and Stress Studies are within the scope of the ICH discussion, not beyond it. The stress studies, which demonstrate that a procedure is stability indicating, are part of the ICH Specificity validation parameter. We feel that the ICH guidances are sufficient, and we question the need for the FDA to add additional detailed information requests. This entire section should be either removed, reworded or greatly condensed.

Lines 441-448 Stress Studies

"Degradation information obtained from stress studies (e.g., products of acid and base hydrolysis, thermal degradation, photolysis, oxidation) for the drug substance and for the active ingredient in the drug product should be provided to demonstrate the specificity of the assay and analytical procedures for impurities. The stress studies should demonstrate that impurities and degradants from the active ingredient and drug product excipients do not interfere with the quantitation of the active ingredient."

PhRMA objects to the level of detail contained on this topic in the draft guidance, and we question the need for such detailed guidance. In particular, the draft guidance language adds confusion to the topic of stress studies.

Stress studies are an extremely complex topic. There is an enormous range of different drug substances and drug products with different characteristics. It is difficult to capture in a single guideline the legitimate and acceptable ways that different companies approach this topic. We feel that the existing ICH guidances are adequate and sufficient. In particular, the ICH Q2B guidance provides clear direction on methodology for analytical method validation stress studies.

This section can be misinterpreted in a fashion inconsistent with ICH guidances as well as other FDA guidances. In such guidances, stressing of drug substance with each of the stressing agents of heat, humidity (where appropriate), acid, base, oxygen, and light is required. However, stressing of drug product with each of the stressing agents of heat, humidity, acid, base, and oxygen is <u>not</u> required. These requirements are discussed in the various relevant guidances: ICH Q1A(R), ICH Q2B, and *FDA Guidance for Industry: Stability Testing of Drug Substances and Drug Products* (Draft, June 1998).

It is our view that the above ICH and FDA guidances provide suitable direction on how to achieve the benefits that can be gained from stressing: information on method specificity, drug substance intrinsic stability, potential degradation pathways, and potential degradation products.

A proscriptive approach to specifying experiments may not be optimal for designing and conducting scientific stress studies. For example, for certain drug products some of the stressing agents (heat, acid, base, oxygen, and light) are not appropriate nor technically reasonable and relevant: base stressing a drug product that is an acidic solution, or light stressing a MDI canister that is impermeable to light. For more complex drug product formulations it may be appropriate to design more detailed studies. Hence experimental design flexibility is needed.

An assessment of the stress study information should provide the rationale for how specificity of the test procedure is ensured. For example, potential interactions between the excipients and the drug substance may be evaluated either from excipient compatibility studies (performed early in development) or from accelerated stability studies of the drug product.

Thus to avoid misinterpretation, PhRMA recommends that the wording be changed to distinguish the difference between stress studies of drug substance and stress studies of drug product:

> "Degradation information obtained from stress studies for the drug substance and for the active ingredient in the drug product should be provided to demonstrate the specificity of the assay and analytical procedures for impurities. If degradation product standards are not available, drug substance should be exposed to the stressing agents of heat, humidity (where appropriate), acid, base, oxygen, and light. For drug product, technically reasonable and relevant stress studies should be performed, which demonstrate that the specificity of the drug product method is ensured. The stress studies should demonstrate that impurities and degradants from the active ingredient and drug product excipients do not interfere with the quantitation of the active ingredient."

FDA should maintain consistency between this FDA guidance and the concepts presented in the above referenced ICH guidances and other FDA guidances (which should be identified in the Line 448 reference). Differing requirements would be of great concern to industry and other regulatory authorities.

Lines 450-453 Submitting Stress Study Results

"The design of the stress studies and the *results should be submitted to the stability section of the application.* Representative instrument output (e.g., chromatograms) and/or other appropriate data (e.g., degradation information obtained from stress studies) *should be submitted in the sections on analytical procedures and controls.*"

PhRMA recommends that these two sentences be reworded to allow a more logical location of information. The design and the results of stress studies that validate the specificity of the test method should be presented in the method validation report, located in the sections on analytical procedures and controls. The design and the results of stress studies for the purpose of determining the drug substance intrinsic stability, potential degradation pathways and potential degradants should be presented in the stability section of the application. Interrelated studies should be fully discussed in one section and cross-referenced by the other section.

The guidance should clarify the minimum information that should be included in the method validation report, such as:

> "The method validation report should discuss the design and the results of stress studies which validate the specificity of the test method. Additionally, the report should include representative instrument output (e.g., chromatograms) and/or other appropriate data, which illustrate the stability-indicating properties of the method."

Line 464-465 Instrument Output/Raw Data: Organic Impurities

" The impurity profile should be assessed at the quantitation limit and the instrument output provided."

This provision should be at the reporting threshold, not the quantitation limit.

Line 483 and Line 498-499 Raw Data (e.g., Integrated peak areas)

PhRMA recommends that FDA delete this phrase and the request for "raw data" throughout the draft guidance. We question the need for integrated peak areas in all chromatographic test procedures. For other types of test procedures, the term "raw data" is poorly defined. The correctness of specific calculations based on raw data is better addressed at time of pre-approval inspection.

Line 506 Raw Data at the Latest Available Time Point

"At a minimum, the submission should include instrument output and raw data for release testing and at the latest available time point for the same batch."

There is no scientific rationale for requiring that the drug product raw data at the latest available stability time point be in the submitted validation report. The validation report should contain representative instrumental output (chromatograms).

The drug product results at the latest available stability time point should be included in the stability section of the application.

The requirement to include the raw data at the latest available stability time point in the validation report would introduce unnecessary redundancy and delay the preparation and review of the application.

Line 534- 545 Table 1. Recommended Validation Characteristics of the Various Types of Tests

PhRMA recommends that FDA replace this table with the original Table exactly as shown in the approved ICH Q2A guideline. Modification of the ICH table will reduce the value of harmonization, and create confusion as to the requirements.

Lines 547-557 Identification

Much of this section is related to specifications, not method validation. Specifications are covered by ICH Q6A guidance and this section should simply refer to Q6A. In particular, the need for a chiral identity method in drug product seems to be different in this guidance than what is stated in ICH Q6A.

PhRMA recommends that FDA remove this section to maintain consistency with ICH Q6A.

Line 599-603 Data Analysis Procedures in a Method Validation Protocol

"Statistical analysis (e.g., linear regression analysis, relative standard deviation) of methods validation data is often used to demonstrate the validity of the method. The statistical procedures for the analysis of the validation data should be determined prior to the start of any validation study. The procedure followed, including the amount of data to collect and the criteria used in determining the acceptability of the analytical procedure, should be specified.

The raw methods validation data and statistical procedures used to analyze the raw data should be provided and discussed in the sections on analytical procedures and controls."

PhRMA strongly disagrees with the general implication that a protocol is required for method validation studies. That approach ignores the scientific process involved in the development and validation of methods for new drugs. Analytical procedures must be validated for their intended purposes according to the principles of good science and the guidance provided in ICH Q2A and Q2B. Internal guidelines for achieving these goals are often useful, but strict acceptance criteria and requirements for the amount of data to collect would only add an unnecessary compliance burden. Also, they would not improve the quality of the analytical validation studies. Such restrictions fail to recognize that in doing scientific studies, one cannot always predict their outcome. The scientist needs the ability to alter the experimental design to prove or disprove the validity of the analytical procedures.

PhRMA does recognize the value of establishing acceptance criteria when a method is transferred from one analytical laboratory to another. For example, once a method is fully developed and validated in an R&D laboratory, transfer of that method to an analytical laboratory at the commercial manufacturing site might often occur under a defined protocol. The protocol might specify the analytical method, the amount of validation data to collect, the statistical procedures for the analysis of the validation data, and the criteria used to determine the acceptability of the analytical procedures at the receiving site.

The need to include raw methods validation data seems unnecessary. Raw data for all calculations cannot be included in a submission, since the documents would be excessively long. The correctness of specific calculations based on raw data is better addressed at time of pre-approval inspection.

Linear regression calculations, RSD and other data analysis tools are commonly used to evaluate methods validation data. They are available in well-tested software and in hand held calculators. A complete description of any other statistical procedures used to analyze the raw data should be provided.

PhRMA recommends that FDA revise this section as follows:

"Statistical analysis (e.g., linear regression analysis, relative standard deviation) of methods validation data is often used to demonstrate the validity of the method. Statistical procedures that are not available in well-tested commercial software, and are used for the analysis of the validation data, should be described in the validation report.

Statistical procedures used to analyze the data within a test procedure should be provided as described in section I. Calculations."

Line 836-847 System Suitability Parameters

"Each analytical procedure submitted should include an appropriate number of system suitability tests defining the critical characteristics of that system. Criteria for all system suitability testing should be provided. The system suitability tests listed below are defined in CDER's reviewer guidance on Validation of Chromatographic Methods (November 1994).

- Tailing factor
- Relative retention
- Resolution
- Relative standard deviation (RSD)
- Capacity factor
- Number of theoretical plates"

We feel that this current draft guidance should supersede and not reference back to previous guidance. The glossary should incorporate the definitions of each term.

Only two or three of the system suitability tests in this list are applicable for procedures submitted in an application. Normally, the Resolution and RSD (and often a Tailing factor) are essential at this stage. We do not agree that Number of theoretical plates should be included in this list. Some parameters should be considered during the development of the method, and should not be routine system suitability controls in an application.

Line 862-863 HPLC Operating Parameters

"The sequence of injection of blanks, system suitability standards, other standards, and samples should be defined."

This is a request for more detail than is necessary. A site standard operating procedure usually covers the sequence of injection. It should only be necessary or critical for the method. It should not be part of the method unless specifically required.

Line 985-993 Enantiomeric Purity

The reporting of enantiomeric purity should be in terms of the weight percentage of undesired enantiomers relative to the desired enantiomer rather than as "enantiomeric excess". This would be consistent with the way chiral impurities are reported using chiral separation procedures.

Lines 1238-1293 Glossary

PhRMA recommends that FDA add clear definitions for the following terms, as discussed elsewhere:

In-house Primary Standard
Primary Reference Standard
Secondary Reference Standard [to replace the term "Working Standard"]
Raw Data (Instrument Output)
Reporting Threshold (Level)
System Suitability Parameters [several]

For clear definition of the terms instrument output/data or raw data, several appropriate examples will be needed so applicants know what type of information is being requested.

Enclosure

Editorial Comments:

The terms "degradant" and "degradation product" are both used in the guideline. Please use the term "degradation product" exclusively (replacing "degradant").

PhRMA prefers to use the term "Analytical Scientist" instead of "analyst". Please use "Analytical Scientist" throughout the guidance.

Line 65-66

"The methods validation process for analytical procedures begins with the planned and systematic collection by the applicant of the validation data to support the analytical procedures."

This sentence should be deleted to avoid confusion, since it adds no value to the discussion. The term "planned and systematic collection... of validation data" may be misinterpreted.

Line 91-92 Background on methods validation

"Each quantitative analytical procedure should be designed to minimize assay variation."

This sentence is unnecessary, does not fit with the context of the section and should be deleted.

Line 175 and Line 805 HPLC

The term "high-pressure liquid chromatography" is incorrect. Please change it to "high-performance liquid chromatography".

Line 187 Physical form

"A physical description of the material, including its color and physical form. "

The term "physical form" may be confused with polymorphic forms. Please change it to the term "physical state".

Line 192 Characterization of Reference Standards

"A detailed description of the analytical procedures used to characterize the reference standard"

Please omit the word "detailed" from the above sentence. A detailed description should not be needed.

Line 249

Please add a hyphen to the term "reversed-phase".

Line 258 Instrument type

"A listing of all equipment (e.g., instrument type, detector, column type, dimensions) should be included, "

Please change "instrument type" to "instrument type or technique". The exact instrument manufacturer should not be specified unless it is critical to the method.

Lines 265-266 Reagents

"A list of reagents and their grades (e.g. USP/NF, American Chemical Society (ACS) Analytical reagent) should be included."

The exact grade of reagents should not be specified unless the grade is critical to the method. Unnecessarily restricting the grade would cause unnecessary burden to foreign labs that might not be able to get the exact same grade of reagents. Please remove the information within the parenthesis.

Line 307-310 Representative Calculations

"Representative calculations, with a tabulation defining all symbols and numerical factors, and specific instructions for the calculation of degradation products and impurities should be included. Any mathematical transformations or formulas used in data analysis should be described in detail."

The wording of the guidance should be revised to clarify the term "representative calculations". The need to include example calculations using submitted raw data seems unnecessary. A complete description of the formula used within the test procedure to obtain a result should be provided.

Additionally, standard calculations commonly used in hand held calculators or commercially available spreadsheet software should be excluded, as their description would result in excessively detailed test procedures.

Lines 317-319 Reporting of Results

"The format used to report results (e.g. percent label claim, weight/weight, weight/volume, parts per million (ppm)) including the specific number of significant figures to be reported should be provided."

PhRMA recommends that FDA revise the wording to:

> "The format used to report results (e.g. percent label claim, weight/weight, weight/volume, parts per million (ppm)) should be provided. Results should be reported in a manner consistent with the specifications such that conformance to those specifications can be readily assessed."

Line 327-328 Setting DL or QL

"The DL or QL can be set using the drug substance's detection response."

As stated in the earlier discussion of "Reporting of Impurities Results", DL and QL should be removed from this section on analytical procedures. The DL and QL should be reported in the methods validation report.

Line 436 Robustness

"In cases where an effect is observed, representative instrument output (e.g., chromatograms) should be submitted."

We believe that it should be unnecessary to provide detailed data such as chromatograms for all robustness experiments. The methods validation report should state where the method is sensitive to changes in method conditions, or which conditions are critical to proper functioning of the method. Here, tabulated system-suitability data are often given to support the statements made. However, we do not provide instrument output such as chromatograms for each experiment done. For comprehensive robustness testing, this would mean providing a quantity of instrument output data for method conditions that are not typical.

PhRMA recommends that this sentence be rephrased as:

"In cases where an effect is observed, the effect should be described and supported by summary data."

Line 460 Organic Impurities

"Representative data for residual solvents are generally not needed."

This sentence seems out of place in the paragraph. It should be placed at the end of section i. Organic Impurities.

Line 465-469 Late-Eluting Impurities

"Additional information should be provided to confirm that the impurity profile is adequately characterized. For example, a representative chromatogram using detection at a low wavelength, such as 205 nm, and double the proposed total run time could be submitted to support the specificity of the analytical procedure."

Guidance provides one approach to looking for late eluting peaks, which may be of limited utility. The experiment will not support "specificity" (the ability to assess unequivocally the analyte in the presence of other components) for the API as indicated. There are several better scientific approaches. This example should be deleted.

It is agreed that studies should be conducted during validation to ensure that there are no potential late-eluting impurities.

Lines 493-494 and 508-512 Detailed Batch Information

"The analytical procedure number, batch number, manufacturing date and site, and date of analysis should be provided. "

"In addition, the analytical procedure number, batch number of the drug product, manufacturing date, date of analysis, source and batch number of drug substance, manufacturing site, and container/closure information should be provided."

There is no need to provide excessively detailed information in the methods validation report. This information should be included in the batch record. PhRMA recommends that FDA revise the wording to:

"In addition, the analytical procedure number, and the batch number of the drug substance or drug product used in validation studies should be provided."

Line 549-550 Identification

PhRMA recommends adding NMR and Raman to the list provided.

Line 618 Comparative Studies

"Comparative results should be statistically analyzed and discussed and any bias explained."

It is not always practical or necessary to statistically analyze all comparative data, for all types of test procedures. PhRMA recommends that FDA delete this expectation.

Line 625 Statistics

More specific references, or no references at all, are preferred.

Line 639

Add a comma after "If during each use,...

Line 702 Material Safety Data Sheets

The MSDS for common analytical reagents (such as common organic solvents for HPLC) should not be required.

Line 765-766 Samples Within 10 Working Days

"When an FDA laboratory contacts the applicant for samples, the applicant should provide FDA laboratories with the samples within 10 working days."

Providing samples to the FDA laboratories within 10 days can cause significant logistic problems when they originate from non-US countries, due to custom declaration, shipping etc. This time should be extended to 20 working days.

Line 779 Review Chemist

Please change the term "validated" to "revalidated".

Line 799 Methodology Section

This section provides guidance on both method validation and instrument calibration for a number of techniques. Reference to calibration requirements for instrumentation is beyond

the scope of the guidance. The use of appropriate system suitability tests for specific techniques ensure that the instrumentation is functioning properly at time of analysis.

Line 823 HPLC Column and Packing Material Parameters

It is unnecessary to specify the frit size and filter type. PhRMA recommends that FDA delete these parameters.

Line 866-868

"Complete details should be provided for the preparation of the mobile phase, including the order of addition of the reagents and the methods of degassing and filtration. The effect of adjustments in mobile phase composition on retention times should be included in the analytical procedure. The rationale for the use of precolumns and/or guard columns should be provided and justified."

It should be only necessary to specify the details of those aspects of the mobile phase preparation which are critical to execute properly. Many details are not critical, as is often determined during the robustness validation studies. (The robustness evaluation belongs in the validation report, not in the analytical procedure.) Line 233 more appropriately states that an analytical procedure "should be described in sufficient detail to allow a competent analyst to reproduce (it)". Thus the paragraph should be revised to replace the phrase "complete details should be provided" with wording from line 233.

Justification should not be required for the use of a guard column. Many laboratories routinely use guard columns to extend column lifetimes. PhRMA recommends that FDA delete the last sentence.

Line 881-886 Column for Gas Chromatography

It is unnecessary to describe the external diameter of the column.

Line 1026 Size Exclusion Chromatography

SEC is not a suitable method for the determination of particle size. SEC yields information about the size/shape of single molecules in solution. This method should be deleted.

Line 1049

"A dissolution test consists of a dissolution procedure and method of analysis (automated on-line analysis or manual sampling followed by HPLC analysis)."

The wording within the parenthesis should be expanded: "automated on-line analysis or manual sampling, followed by UV or HPLC analysis".

Line 1091 FDA Laboratory Automation

"The use of automated analytical procedures, although desirable for control testing, may lead to delay in regulatory methods validation because FDA laboratories have to assemble and validate the system before running samples. To avoid this delay, applicants should demonstrate the equivalence of a manual procedure to the automated procedure based on the same principle whenever possible."

An FDA laboratory should be equipped with suitable technology including automation that is the current industry standard

Line 1113-1125 Information Included in the Methods Validation Package and the Stability Section

These lines appear to be inaccurate, with incorrect references. Also, it seems unnecessary to require data for both the initial sample and the oldest sample of a batch. PhRMA recommends that FDA revise these lines in light of the earlier comments discussed.